

REMARKS

Claims 16, 17 and 18 are amended. Claim 16 has been amended to include an additional alkaloid, which is described in the published application at ¶ 0033. Claims 17 and 18 were amended merely to remove "the alkaloid" from the claims to avoid redundancy. Claims 1-18 and 21-24 are currently pending.

35 U.S.C. § 103(a)

Claims 1-3, 6, 8-18, and 21-24 remain rejected for allegedly being obvious over Kirby *et al.* (U.S. Patent No. 6,444,234; herein, "the '234 patent") in view of WO02/40033 (herein, "the '033 application"). See the Office Action at page 3.

Applicants respectfully maintain their traversal of this ground for rejection.

In response to Applicants' arguments on this point, the Examiner responded by pointing to the teachings of ('033) which discloses that phosphate derivative of electron transfer agent may exist in the form of a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl group or a complex with a complexing agent selected from amphoteric surfactant, cationic surfactant or aminoacids (*sic.*) having nitrogen functional groups or proteins rich in these amino acids (see page 4, lines 8-11 and claim 4). Taking chemistry into consideration it can be said that since phosphate derivatives of tocopherol has been shown to form complex with aminoacids (*sic.*) having **nitrogen functional groups**, the **nitrogen** is the critical element in forming a complex with tocopherol phosphate (Office action at page 9, emphasis in original).

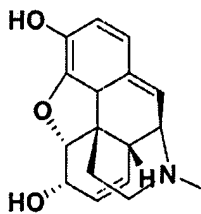
The Examiner concludes that "it would have been obvious to one of ordinary skill in the art to use the phosphate derivatives of tocopherol to form a complex with an alkaloid such as morphine which bears a functional nitrogen." See the Office Action at pages 9 and 10.

Based on a review of the record, this appears to be the first time the Examiner has relied on nitrogen as a "critical element" and one motivating the combination of the '234 patent and the '033 application. Applicants respectfully disagree.

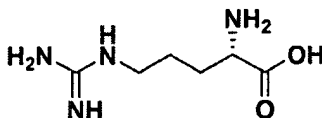
The complexing agents of the '033 application may have some feature in common with the alkaloids required by the present claims. However, the Examiner simply may not hunt for that feature using Applicants claims as a guide. The motivation required for obviousness cannot be found after the fact.

Further, as recognized by the Examiner, the '033 application teaches that phosphate derivatives of electron transfer agents can form a complex with a complexing agent selected from amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups or proteins rich in these amino acids. *Some of the compounds suitable as complexing agents do not have nitrogen functional groups.* For example, phosphonium and sulfonium compounds are known cationic surfactants that do not have nitrogen functional groups. Thus, it cannot be said that nitrogen is the critical element in forming a complex with phosphate derivatives of electron transfer agents.

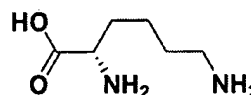
The '033 application teaches only that when a phosphate derivative of an electron transfer agent forms a complex with an amino acid, *the amino acids* need to have nitrogen functional groups. There is no teaching that any chemical compounds having a nitrogen atom can form a complex with a phosphate derivative of an electron transfer agent. One of ordinary skill in the art would know that an amino acid having a nitrogen functional group (*e.g.*, arginine or lysine) would be structurally and chemically different from other chemical compounds containing a nitrogen atom (*e.g.*, morphine; see the structures below). Typically, amino acids contain amino and carboxylic acid groups, which would lead to different chemical activities from the compounds without the groups. As such, the '033 application does not teach or suggest that phosphate derivatives of electron transfer agents would form a complex with any chemical compounds containing a nitrogen atom. And one of ordinary skill in the art would not assume as much.



Morphine



Arginine



Lysine

In addition, even a phosphate derivative of electron transfer agents could form a complex with a non-amino acid chemical compound, one of ordinary skill in the art would not expect that

the complex would enhance transdermal activity of that compound. Applicants would like to point out that the '033 application discloses the delivery of electron transfer agents (*e.g.*, tocopherol) through a complex formed with complexing agents including amphoteric surfactants, cationic surfactants or amino acids. The '033 application does not teach or suggest how to deliver amphoteric surfactants, cationic surfactants or amino acids having nitrogen functional groups. In other words, the '033 application cannot teach or suggest how to enhance transdermal activity of morphine as the Examiner appears to argue that morphine can be used to form a complex instead of an amino acid having nitrogen function groups.

Further, the '033 application teaches, as exemplified in Example 2, that a complex can be prepared in water/ethanol solution (87.5 w/w% of the 95/5 water/ethanol mixture). The '234 patent, however, discloses that the solvent system in the disclosed formulation is generally non-aqueous as shown in the table of column 16. When water may be used for water soluble active agents, it will usually constitute less than about 50%. See column 10, lines 16-28. Clearly, the complexes disclosed in the '033 application and the '234 patent are prepared in two different solvent systems. One of ordinary skill in the art would not be motivated to combine these two references to arrive at the present invention.

In view of the foregoing, the Examiner is asked to withdraw this ground for rejection.

Claims 4, 6, and 7 also remain rejected as being obvious over Schor *et al.* (U.S. Patent No. 4,369,172, herein "the '172 patent") in view of the '033 application (Office Action at page 6).

Claims 4, 6, and 7 depend, directly and indirectly, on claim 1 which has been discussed above.

The '172 patent discloses a carrier material which can be combined with active ingredients to prepare an oral or buccal formulation, or a tablet. But it fails to suggest or motivate the use of this material to specifically combine with morphine in a formulation. As defined in the specification at column 5, lines 43 to column 7, lines 21, the active ingredient can be any one from the long list including a variety of drugs for treating various diseases. It cannot motivate one of ordinary skill in the art to modify the '033 application formulation by (1) picking out morphine from the long list shown at columns 5-7, and (2) combining it with a phosphate

Applicant : West, *et al.*
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Filed : June 29, 2006
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Associate's Reference No.: RS: P63379 US

derivatives of electron transfer agents in the '033 application in order to prepare the formulations of claims 4, 6, and 7.

Claim 5 remains rejected as being obvious over the '172 patent in view of the '033 application and further in view of Fish *et al.* (U.S. Patent Application No. 2004/0234602, herein "the '602 application").

Claim 5 depends indirectly from claim 1, which has been discussed above.

As noted above, the '172 patent and the '033 application do not motivate one of skill in the art to combine these two references to arrive at the formulations claimed. While the '602 application discloses a composition with an enteric coating, this addition to the previous two references cannot make the present invention obvious.

In view of the foregoing, Applicants request the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

Filed herewith is a Petition for Extension of Time. Please apply any charges or credits to deposit account 06-1050.

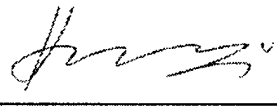
Respectfully submitted,

Date: _____

March 07, 2008

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